Osteoarthritis and Cartilage 21 (2013) 1214–1222

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Relationship between knee pain and the presence, location, size and phenotype of femorotibial denuded areas of subchondral bone as visualized by MRI

S. Cotofana †‡*, B.T. Wyman §, O. Benichou ||, D. Dreher ¶[a], M. Nevitt #, J. Gardiner §, W. Wirth †‡, W. Hitzl †, C.K. Kwoh ††, F. Eckstein †‡, R.B. Frobell †‡‡ For the OAI Investigators Group

† *Paracelsus Medical University, Salzburg, Austria*
‡ *Chondrometrics GmbH, Ainring, Germany*
§ *Pfizer Inc., Groton, CT, USA*
|| *Eli Lilly & Co, Indianapolis, IN, USA*
¶ *Merck Serono, Geneva, Switzerland*
# *UCSF, San Francisco, CA, USA*
†† *University of Pittsburgh & VA Pittsburgh Healthcare System, PA, USA*
‡‡ *Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden*

ARTICLE INFO

Article history:
Received 14 May 2012
Accepted 9 April 2013

Keywords:
Pain
Cartilage
MRI
Denuded area of subchondral bone

SUMMARY

Objective: Conflicting associations between imaging biomarkers and pain in knee osteoarthritis (OA) have been reported. A relation between pain and denuded areas of subchondral bone (dABs) has been suggested and this study explores this relationship further by relating the presence, phenotype, location and size of dABs to different measures of knee pain.

Methods: 633 right knees from the Osteoarthritis Initiative (OAI) (250 men, age 61.7 ± 9.6 yrs, BMI 29.4 ± 4.7 kg/m^2) were included. Manual segmentation of the femorotibial cartilage plates was performed on 3 T coronal fast low angle shot with water excitation (FLASHwe) images. dABs were defined as areas where the subchondral bone was uncovered by cartilage. The following measures of pain were used: weightbearing-, non-weightbearing-, moderate-to-severe-, infrequent- and frequent knee pain.

Results: Using pain measures from subjects without dABs as a reference, those with at least one dAB had a 1.64-fold higher prevalence ratio [PR, 95% confidence interval (CI) 1.24–2.18] to have frequent and 1.45-fold higher for moderate-to-severe knee pain (95% CI 1.13–1.85). Subjects with dABs in central subregions had a 1.53-fold increased prevalence of having weightbearing pain (95% CI 1.20–1.97), especially when the central subregion was moderately (>10%) denuded (PR 1.81, 95% CI 1.35–2.42). Individuals with cartilage-loss-type dABs had a slightly higher prevalence (PR 1.13, 95% CI 1.00–1.27) of having frequent knee pain compared to individuals with intra-chondral-osteophyte-type dABs.

Conclusion: This study supports a positive relation between femorotibial dABs and knee pain, especially when the dABs are located centrally (i.e., in weightbearing regions) or when the respective central subregion is moderately denuded.

Introduction

Osteoarthritis (OA) accounts for a large proportion of the global disease burden in the industrialized world[1] and is most commonly seen in the knee joint. Among individuals with knee OA, pain is the main reason for seeking medical care[2] however, pain perception is a multifactorial and complex issue[3–7]. Pain in knee OA likely originates from richly innervated structures such as the joint capsule[8], the synovium[9] or the subchondral bone[10] and consequently, pathologies affecting these structures have been suggested to be directly or indirectly related to pain in knee OA[11–15]. Several studies have correlated imaging biomarkers, such as bone marrow lesions (BMLs), meniscal tears or synovitis, to the incidence and the severity of ipsi-lateral knee pain in OA[12,16–21] however, few succeeded in finding significant associations[16,19–21].

* Address correspondence and reprint requests to: S. Cotofana, Institute of Anatomy & Musculoskeletal Research, PMU, Strubergasse 21, A5020 Salzburg, Austria. Tel: 43-662-44-2002-1245; Fax: 43-662-44-2002-1249.
E-mail address: sebastian.cotofana@pmu.ac.at (S. Cotofana).
[a] Present address: Totzke & Dreher Scientific SA, Geneva, Switzerland.

1063-4584/$ – see front matter © 2013 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.joca.2013.04.001

Magnetic resonance imaging (MRI) provides several quantitative structural measures of cartilage morphology[22]. Denuded areas of subchondral bone (dABs) are defined as areas where the subchondral bone is not covered by articular cartilage and was presented as one of the three variables providing independent information on progressive cartilage loss[23]. Previous histopathological and immunohistochemical studies in both animals and humans revealed evidence for the presence of sensory nerve fibres in layers of cartilage next to the subchondral bone[10,24–26]. It was hypothesized, that nerve fibres could be growing from the subchondral bone (along with blood vessels) into the non-calcified cartilage during osteochondral remodelling due to OA progression[24]. The authors suggest that this neurogenesis may represent a new potential source of pain, occurring when subchondral bone is exposed to mechanical stimuli due to a lack of overlaying cartilage. In support, the presence of dABs in OA affected knees was shown to be associated with the prevalence and incidence of knee pain, also after adjustment for BMLs[14]. Our group recently showed a significant positive relationship between the grade of radiographic OA (ROA) and the presence of dABs[27], and this agrees well with the report of a positive relationship between individual radiographic features of OA progression [such as advanced Kellgren and Lawrence grades (KLG)] and knee pain[17].

In a previous report from the sample used in this study, we identified at least two different phenotypes of dABs: cartilage-loss-type and intra-chondral-osteophyte-type (Fig. 1)[27]. We have also shown that dABs occur both in the central (i.e., weightbearing) and the peripheral (non-weightbearing) regions of the knee[27], which may be of importance for knee pain experiences during weightbearing and/or non-weightbearing activities. Thus, the presence, location, size, and phenotype of dABs in the femorotibial joint could lead to different aspects of knee pain experiences in OA.

The objective of this cross-sectional study was therefore to investigate the relationship between the presence, location, size and phenotype of dABs and aspects of knee pain (weightbearing-, non-weightbearing-, moderate-to-severe-, infrequent- and frequent knee pain). We specifically hypothesized that individuals with at least one femorotibial dAB are more likely to experience frequent pain and have a greater risk of reporting moderate-to-severe knee pain than individuals without femorotibial dABs, that individuals with at least one centrally located dAB report more weightbearing knee pain than individuals with peripheral dABs (whereas the location is less important in context of non-weightbearing pain) and that individuals with at least one cartilage-loss-type dAB are more likely to report frequent pain and have a greater risk of having moderate-to-severe pain than subjects with intra-chondral-osteophyte dABs alone.

Methods

Study sample

The Osteoarthritis Initiative (OAI) is a large cohort study aiming to identify biomarkers of OA. The sample analyzed in this study was based on a convenience sample of OAI participants from industry partners, the OAI coordinating centre and an image analysis company (Chondrometrics GmbH). We used baseline knee MRIs from 633 OAI subjects, including participants from the healthy reference cohort, from the progression cohort, and from the incidence cohort. The radiographic grading relied on the baseline calculated KLG, derived from osteophyte and joint space narrowing (JSN) grades as determined by the Osteoarthritis Research Society International (OARSI)-atlas scores assigned by centrally trained and certified readers at the clinical OAI recruitment sites[28]. The study sample and a detailed description of how calculated KLGs were derived have been previously described in detail[27].

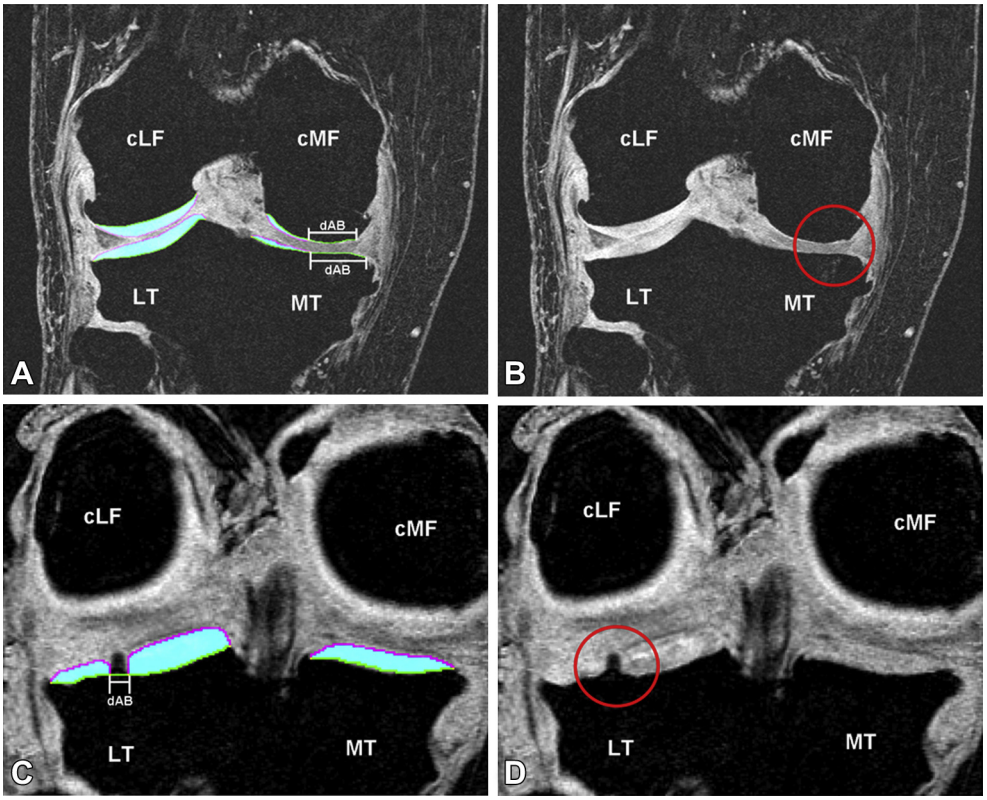

Fig. 1. Different phenotypes of the dABs as visualized quantitatively by MRI cartilage morphometry. (A & B) cartilage-loss-type dAB in the central medial femur (cMF) and medial tibia (MT) with (A) and without (B) segmentation. (C & D) intra-chondral-osteophyte-type dAB in the lateral tibia (LT) with (C) and without (D) segmentation.

In summary: 158 right knees with KL grading, ranging from 0 to 4 from the OAI progression subcohort; 418 right knees with definite radiographic knee OA corresponding to KLG 2 and 3; 13 right knees with radiographic knee OA corresponding to KLG 4; 44 right knees from the healthy reference cohort without symptomatic or radiographic knee OA (corresponding to KLG 0)[27].

Demographic and radiographic data was obtained from the OAI public database (version 0.2.2 for clinical data and version 0.E.1 for the imaging data, www.oai.ucsf.edu). Grading of radiographic OA (ROA) relied on calculated KLG, provided by the OAI and aggregated from the clinical site readings of osteophytes and JSN according to the OARSI atlas for the purpose of recruitment[28]. Table I shows demographic data of the total sample stratified by location and size of the dABs (no dABs, peripheral dABs, central dABs). Knees with central dABs were further divided into mildly denuded (denuded area more than 0% but ≤10% of the respective central cartilage subregions) and moderately denuded (denuded area >10% of the respective central cartilage subregions) as described below.

MRI assessment and analysis

This study relied on the double oblique coronal 3D fast low angle shot (FLASH) images with water excitation (we), acquired in the right knees of all OAI participants in this study[27], as the FLASHwe sequence was appropriately validated for articular cartilage analysis using morphometry, with test–retest precision error for analyzing dABs of 6.8% [expressed as root mean square of standard deviations (SDs)][29–31]. Quality control as well as the manual segmentation process performed at the image analysis centre (Chondrometrics GmbH, Ainring, Germany) was described in detail previously[27,32–34]. Data was handled blinded to the aims of this study and to clinical and radiographic data.

Denuded areas of subchondral bone

dABs represent regions of subchondral bone not covered by articular cartilage. As reported previously in this sample, dABs could be of two types: cartilage loss or intra-chondral-osteophytes (Fig. 1)[27]. Classification of type and number of dABs was performed by two expert readers (SC and RF) in each cartilage plate affected by dAB. Any discrepancies in classifying dABs were resolved immediately in consensus between the two readers[27]. Since both types could occur in one plate (or in one knee) we used the following categories in our analysis:

- Exclusive cartilage-loss-type dABs = plates or knees with dABs originating from only cartilage-loss-type dABs
- Exclusive intra-chondral-osteophyte-type dABs = plates or knees with dABs originating from only intra-chondral-osteophyte-type dABs
- Combined cartilage-loss & intra-chondral-osteophyte-type dABs = plates or knees with dABs originating from a combination of the two types (i.e., cartilage-loss-type and intra-chondral-osteophyte-type dABs).

None of the individual dABs showed a combination of the two types and consequently each individual dAB was of one single type. The size and location of dABs of this sample were determined for each cartilage plate (medial and lateral tibia and central medial and lateral femur) using custom software (Chondrometrics GmbH, Ainring, Germany)[27,32,33]. In brief, dAB size was determined in relation to the area of subchondral bone in each cartilage plate and was expressed in percent. The location was automatically determined in five tibial (central, external, internal, anterior, and posterior), and three femoral (central, external, internal) subregions for the medial and lateral compartment respectively using an algorithm previously described[27,32,35]. The algorithm did however not

Table I
Demographic data, stages of ROA and the presence, location, size and phenotype of dABs in the study sample ($n = 633$). The last two columns show mildly (defined as ≤10% in size of the respective cartilage plate) and moderately denuded (defined as >10% in size of the respective cartilage plate) central dABs

Demographics (total sample size: $n = 633$)*	No dABs ($n = 388$)	Peripheral dABs ($n = 120$)	Central dABs ($n = 125$)	Central dABs mildly denuded ($n = 63$)	Central dABs moderately denuded ($n = 62$)
Age, mean (SD)	60.7 (9.7)	64.2 (8.9)	62.7 (9.4)	61.5 (9.5)	64.0 (9.2)
BMI mean (SD)	29.0 (4.9)	30.4 (4.7)	29.6 (4.0)	29.2 (4.3)	30.0 (3.8)
Sex (male), *n* (%)	130 (33.5)	58 (48.3)	62 (49.6)	33 (52.4)	29 (46.8)
ROA stage†, *n* (%)*	***n* = 388**	***n* = 120**	***n* = 125**	***n* = 63**	***n* = 62**
cKLG 0	46 (11.9)	1 (0.8)	0	0	0
cKLG 1	24 (6.2)	6 (5.0)	4 (3.2)	4 (6.3)	0
cKLG 2	184 (47.4)	51 (42.5)	24 (19.2)	17 (27.0)	7 (11.3)
cKLG 3	131 (33.8)	61 (50.8)	69 (55.2)	37 (58.7)	32 (51.6)
cKLG 4	3 (0.8)	1 (0.8)	28 (22.4)	5 (7.9)	23 (37.1)
Pain measures, *n* (%)*	***n* = 388**	***n* = 120**	***n* = 125**	***n* = 63**	***n* = 62**
Weightbearing knee pain‡	112 (28.9)	39 (32.5)	54 (43.2)	22 (34.9)	32 (51.6)
Non-weightbearing knee pain§	49 (12.6)	19 (15.8)	24 (19.2)	10 (15.9)	14 (22.6)
Infrequent knee pain‖	113 (29.1)	39 (32.5)	33 (26.4)	18 (28.6)	15 (24.2)
Frequent knee pain¶	157 (40.5)	52 (43.3)	77 (61.6)	35 (55.6)	42 (67.7)
Moderate-to-severe knee pain#	96 (24.7)	36 (30.0)	51 (40.8)	25 (39.7)	26 (41.9)
Phenotype of dABs, *n* (%)*	***n* = 388**	***n* = 120**	***n* = 125**	***n* = 63**	***n* = 62**
Exclusive cartilage-loss-type dABs	0	22 (18.3)	36 (28.8)	20 (31.7)	16 (25.8)
Exclusive intra-chondral-osteophyte-type dABs	0	88 (73.3)	36 (28.8)	27 (42.9)	9 (14.5)
Cartilage-loss & intra-chondral-osteophyte-type dABs combined	0	10 (8.3)	53 (42.4)	16 (25.4)	37 (59.7)

* Significant difference between groups using Kruskal–Wallis (age, BMI) or Pearson Chi-Squared test (sex, ROA stage, pain measures and dAB phenotype); $P < 0.05$.
† Assessed by calculated KLG.
‡ At least moderate pain in one of the WOMAC items: stand, stair, walk.
§ At least moderate pain in one of the WOMAC items: sit, lie.
‖ Knee pain in the past 12 months, but not in most days of a month.
¶ Knee pain in most days of a month in the past 12 months.
# At least 4 in the NRS ranging from 0 to 10.

differentiate between one single or several dABs. We defined central dABs as dABs affecting one of the four central femorotibial subregions [central medial and lateral tibia (cMT, cLT) and central medial central femur and central lateral central femur (ccMF, ccLF)] with dAB > 0%. Respectively, a dAB was classified as peripheral, when NOT affecting one of the four central subregions (dAB = 0% in cMT, cLT, ccMF, ccLF). DABs affecting both subregions (f.i. marginally located) were classified as central dAB, when dAB > 0% in cMT, cLT, ccMF, ccLF, disregarding the extent of affection of the neighbouring peripheral subregion[27,35] (Fig. 3).

To investigate the influence of size of dABs in the central subregions of knees with definite dABs, we applied a 10% threshold to classify between mildly *versus* moderately denuded central subregions. In knees with definite central dABs, the central subregion was considered as moderately denuded when >10% of the respective cartilage subregion was denuded and mildly denuded when ≤10% of the respective cartilage subregion was denuded[27].

Assessment of pain measures

Measures of knee pain were obtained from the OAI database (version 0.2.2) and since all MR images were from right knees, only pain measures from the right knee were used.

Weightbearing and non-weightbearing pain were assessed using the pain subscore items of the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC)[36]. In agreement with previous publications[15,37], we used the three pain subscore items: "pain during climbing stairs"; "pain during walking"; "pain during standing" to assess weightbearing pain and the two pain subscore items: "pain during sitting"; "pain during lying in bed" to assess non-weightbearing pain. A score of at least 2 (i.e., moderate pain) for each item was regarded as a positive outcome and a score of less than 2 in any of the items was regarded as a negative outcome. Positive outcomes for all respective items were regarded as having weightbearing or non-weightbearing knee pain whereas at least one negative outcome in any of the items was regarded as not having weightbearing or non-weightbearing knee pain[15].

Pain severity was evaluated using the numerical rating scale (NRS) where subjects were asked to grade their knee pain severity during the last 30 days ranging from 0 (no pain) to 10 (pain as bad as you can imagine). In agreement with previous reports, we defined the presence of moderate-to-severe knee pain as 'yes' if the answer was ≥4 or 'no' if the answer was <4[14,38].

Pain frequency was evaluated using the OAI "baseline symptom status assessment of the right knee" (P01RKSX, www.oai.ucsf.edu): 0 (no pain in past 12 months); 1 (pain in past 12 months but not most days of a month); 2 (pain most days of a month in the past 12 months). We defined 1 as infrequent knee pain and 2 as frequent knee pain.

Statistical analysis

All statistical analyses were performed using PASW 18 (SPSS Inc, Chicago, IL). To evaluate the relation between different aspects of knee pain and dABs we used Poisson-regression-models with robust variance estimator (Huber/White/sandwich estimator) to calculate the prevalence with adjustment for age, sex and body mass index (BMI). Results are presented as prevalence ratio (PR) in combination with the 95% confidence intervals (CIs). Kruskal–Wallis test was used for comparisons of independent test samples for variables deviating from a normal distribution. Pearson's Chi-Squared tests were used to analyze crosstabulation tables. A significant relation was reported for *P*-values less than 5%. Further, a *post-hoc* approach for multiple testing using Bonferroni correction was conducted when estimating the PR for dAB phenotype ($P < 0.0125$) and dAB location ($P < 0.0025$).

Results

The knees included in this analysis represent a broad spectrum of the severity of ROA with most knees having mild to moderate ROA. Individuals without dABs in their analyzed knee comprised the control group ($n = 388$), including 44 individuals from the OAI healthy

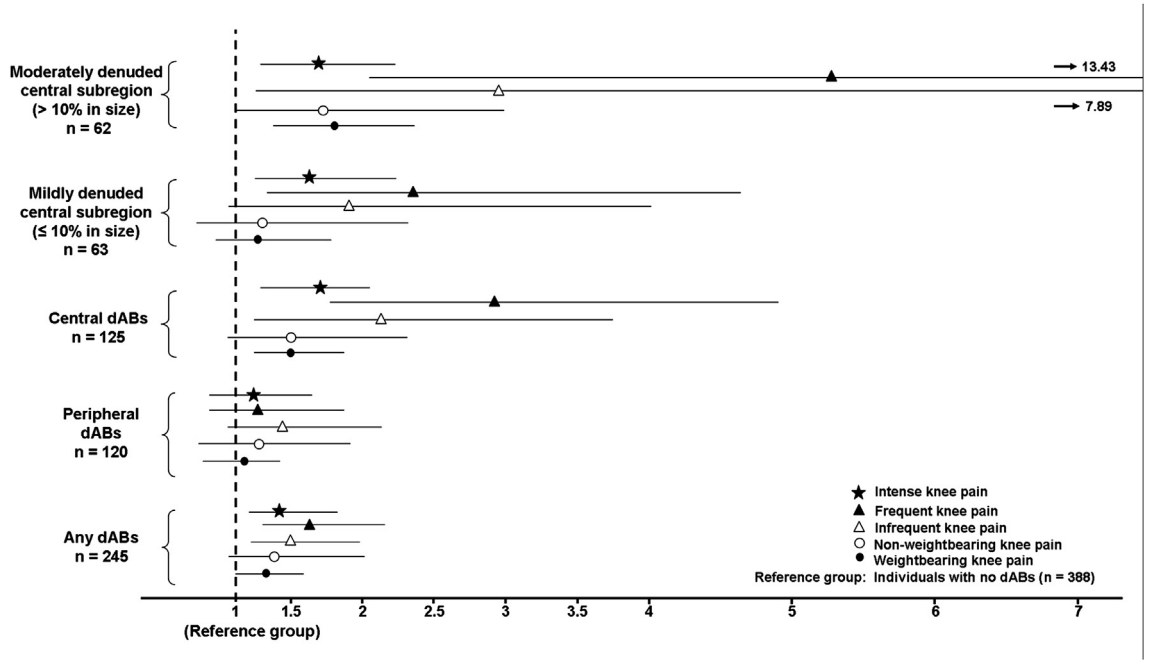

Fig. 2. Adjusted (age, sex, BMI) PR and the 95% CI for: ● = "weightbearing" knee pain; ○ = "non-weightbearing" knee pain; ▲ = "frequent" knee pain; △ = "infrequent" knee pain and ▲ = "moderate-to-severe" knee pain in subjects with at least one femorotibial dAB ($n = 245$), peripheral dABs ($n = 120$), central dABs ($n = 125$), mildly denuded central subregions (≤10% of the subchondral bone area, $n = 63$) and moderately denuded central subregions (>10% of the subchondral bone area, $n = 62$). Bars display the upper and lower 95% CIs. Reference category (set as 1) is those without femorotibial dABs ($n = 388$).

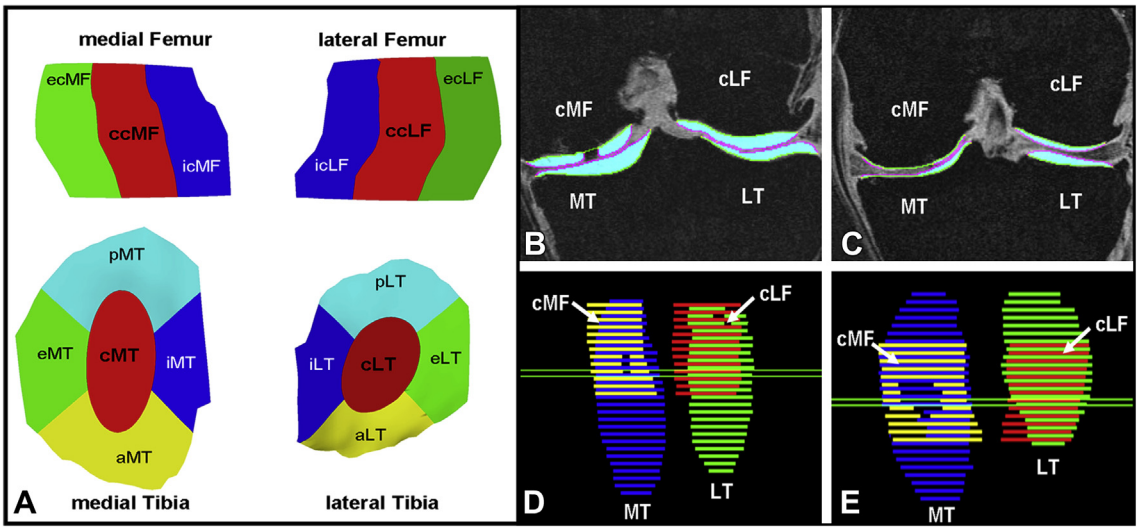

Fig. 3. The femorotibial regions and subregion. (A) Showing the four femorotibial medial and lateral tibia (MT, LT) and (medial and lateral) central femur (cMF, cLF) and the 16 femorotibial subregions (10 tibial and six femoral): external, central, internal, anterior and posterior medial and lateral tibia (eMT, cMT, iMT, aMT, pMT and eLT, cLT, iLT, aLT, pLT) and external, central, internal central medial and lateral femur (ecMF, ccMF, icMF and ecLF, ccLF, icLF). The central subregions are highlighted in bold. (B) Showing an intra-chondral-osteophyte-type dAB in the central cMF. (C) Showing a cartilage-loss-type dAB in the central cMF (and MT). (D) Overview of the segmentation displayed in (B), showing the intra-chondral-osteophyte-type dAB in the central cMF comprising less than 10% of the central subregion. Additionally a small peripheral dAB can be seen in the posterior lateral tibia. (E) Overview of the segmentation displayed in (C), showing a cartilage-loss-type dAB affecting the central cMF and the external cMF but comprising more than 10% of the central subregion.

reference cohort with bilateral KLG0 and no risk factors of knee OA. In this group, 112 (28.9%) reported weightbearing knee pain, 49 (12.6%) non-weightbearing knee pain, 96 (24.7%) moderate-to-severe knee pain, 113 (29.1%) infrequent knee pain and 157 (40.5%) frequent knee pain, whereas the subset from the healthy reference cohort reported no pain in all of the measured pain estimates. Two hundred and forty-five participants had at least one dAB in their analyzed knee, with 125 (19.8%) of those having central dABs and with 62 (9.8%) having moderately denuded central dABs. Of those 93 (38%) reported weightbearing knee pain, 43 (18%) non-weightbearing knee pain, 87 (36%) reported moderate-to-severe knee pain, 129 (53%) frequent knee pain and 72 (29%) reported infrequent knee pain (Table I).

Pain relationships in those with at least one dAB versus those without any dABs

Compared to those without dABs in the femorotibial joint (Fig. 2), participants with at least one femorotibial dAB had a higher prevalence to report weightbearing knee pain (PR 1.29, 95% CI 1.03–1.61), moderate-to-severe knee pain (PR 1.45, 95% CI 1.13–1.85), infrequent knee pain (PR 1.50, 95% CI 1.11–2.03) and frequent knee pain (PR 1.64, 95% CI 1.24–2.13). The prevalence of non-weightbearing knee pain was not significantly higher in those with at least one femorotibial dAB, compared to those without dABs (PR 1.37, 95% CI 0.93–2.01). Compared to those without dABs, those with at least one dAB in the central subregions were more prevalent to have weightbearing knee pain (PR 1.53, 95% CI 1.20–1.97), moderate-to-severe knee pain (PR 1.67, 95% CI 1.27–2.19), infrequent knee pain (PR 2.11, 95% CI 1.20–3.71) and frequent knee pain (PR 2.93, 95% CI 1.74–4.94) (Fig. 2). No statistically significant relationship for any pain measure was found between participants with only peripheral dABs when compared to participants without any dABs ($P > 0.11$; Fig. 2).

Pain relationships with regard to location, size and phenotype of dAB in those with dABs

Using individuals with peripheral dABs as reference, individuals with at least one central dAB had a higher prevalence of having

Table II
Relationship between location (peripheral vs central) and size (mildly vs moderately denuded) of dABs within those with dABs ($n = 245$). Values are presented as PR with adjustment for age, sex, BMI. The last two columns show mildly (defined as ≤10% in size of the respective cartilage plate) and moderately denuded (defined as >10% in size of the respective cartilage plate) central dABs

Pain measures	Reference: peripheral dABs* ($n = 120$)	Central dABs† ($n = 125$) PR (95% CI)	Mildly denuded central subregion‡ ($n = 63$) PR (95% CI)	Moderately denuded central subregion§ ($n = 62$) PR (95% CI)
Weightbearing knee pain	1	1.40 (1.02–1.93)	1.20 (0.80–1.81)	1.62 (1.15–2.30)
P-value (crude)		0.039	0.382	0.006
Non-weightbearing knee pain	1	1.29 (0.74–2.24)	1.80 (0.54–2.18)	1.49 (0.80–2.77)
P-value (crude)		0.386	0.827	0.206
Moderate-to-severe knee pain	1	1.41 (1.01–1.97)	1.43 (0.97–2.11)	1.41 (0.94–2.11)
P-value (crude)		0.046	0.071	0.094
Infrequent knee pain	1	1.08 (0.94–1.23)	1.01 (0.88–1.17)	1.20 (0.94–1.54)
P-value (crude)		0.279	0.845	0.151
Frequent knee pain	1	1.19 (1.06–1.34)	1.11 (0.97–1.27)	1.48 (1.19–1.85)
P-value (crude)		0.004	0.133	<0.001

* Knees with at least one dAB not including a central subregion in any of the four cartilage plates.
† Knees with at least one dAB affecting one central subregion of the femorotibial joint.
‡ Knees with at least one dAB affecting at least one central subregion where ≤10% of the central subregion is denuded (mildly denuded).
§ Knees with at least one dAB affecting at least one central subregion where >10% of one central subregion is denuded (moderately denuded).

Table III
Relationship between size (mildly vs moderately denuded) of centrally located dABs within those with central dABs exclusively ($n = 125$). Values are presented as PR with adjustment for age, sex, BMI

	Reference: Mildly denuded central subregions* ($n = 63$)	Moderately denuded central subregions† ($n = 62$) PR (95% CI)
Weightbearing knee pain	1	1.45 (0.97–2.18)
P-value (crude)		0.071
Non-weightbearing knee pain	1	1.46 (0.70–3.02)
P-value (crude)		0.313
Moderate-to-severe knee pain	1	1.07 (0.71–1.61)
P-value (crude)		0.766
Infrequent knee pain	1	1.07 (0.95–1.21)
P-value (crude)		0.275
Frequent knee pain	1	1.11 (0.99–1.24)
P-value (crude)		0.073

* Knees with at least one dAB affecting at least one central subregion where ≤10% of the central subregion is denuded (mildly denuded).
† Knees with at least one dAB affecting at least one central subregion where >10% of one central subregion is denuded (moderately denuded).

weightbearing knee pain (PR 1.40, 95% CI 1.02–1.93), moderate-to-severe knee pain (PR 1.41, 95% CI 1.01–1.97) and frequent knee pain (PR 1.19, 95% CI 1.06–1.34) (Table II). Further, those with at least one moderately denuded central subregion had a higher prevalence to report weightbearing pain (PR 1.62, 95% CI 1.15–2.30) and frequent knee pain (PR 1.48, 95% CI 1.19–1.85) (Table II) compared to individuals with peripheral dABs.

No statistical significant relationships were seen between individuals with mildly denuded central subregions compared to individuals with moderately denuded central subregions. However, a trend was visible for individuals with moderately denuded central areas towards a higher prevalence of reporting weightbearing and frequent knee pain (Table III).

With regard to dAB phenotypes, participants with combined cartilage-loss-type and intra-chondral-osteophyte-type dABs in the femorotibial joint had a slightly higher prevalence of reporting frequent knee pain compared to individuals with exclusive intra-chondral-osteophyte-type dABs (PR 1.13, 95% CI 1.00–1.27, not significant after correction for multiple testing) (Table IV).

On the cartilage plate level, individuals with a dAB in the central medial femur (PR 1.22, 95% CI 1.08–1.38) and in the lateral tibia (PR 1.15, 95% CI 1.02–1.30, not significant after correction for multiple testing) had an increased prevalence to report frequent knee pain. Remarkably, individuals with a dAB in the central lateral femur were less prevalent to report non-weightbearing knee pain (PR 0.51, 95% CI 0.26–0.97, not significant after correction for multiple testing) compared to those with a dAB in any other plate (Table V).

Discussion

To our knowledge, this is the first study to assess the cross-sectional relationship between the presence, location, the size and the phenotype of femorotibial dABs and different aspects of knee pain. Using a larger sample, this study confirms a positive relation between femorotibial dABs and ipsi-lateral knee pain, previously shown by Moisio *et al.*[14] In extension of that report however, our results also suggest that those with at least one dAB report more weightbearing pain, but not more non-weightbearing knee pain, than subjects without dABs and that individuals with central dABs (i.e., dABs affecting at least one weightbearing subregion) report more weightbearing, moderate-to-severe, and frequent knee pain than those with peripheral dABs, especially when more than 10% of the central subregion was denuded.

This study has certain limitations. First, cross-sectional pain assessment is a challenge, mainly due to the large individual variation influenced by multiple endogenous and exogenous factors in the subjective pain experience[3–7]. However, we used a standard definition for the assessment of frequency of knee pain, a previously published strategy to assess knee pain during (femorotibial) weightbearing and non-weightbearing conditions, and an established classification for the absence/presence of moderate-to-severe knee pain[15,37,38]. It is noteworthy, that pain during sitting, classified here as non-weightbearing knee pain, could originate from femoropatellar joint disease but evaluation of the femoropatellar compartment was technically not possible from a coronal FLASHwe imaging protocol, which was the basis of the current analysis. Secondly, dAB is an MR imaging finding derived from manual segmentation of cartilage and subchondral bone and may not directly relate to clinically relevant findings reported by experienced radiologists or to focal chondral defects seen at arthroscopy. Thirdly, the MR sequence used here (FLASHwe) does not adequately visualize other relevant joint pathologies, such as BMLs, meniscal tears or synovitis, previously shown to have a relation to knee pain in OA[12,16–21]. However, appropriate sequences were acquired by the OAI but since we concentrated on the FLASHwe sequence we lack information on other joint pathologies and have not assessed their potential relation to pain in this sample. Future work is needed to light up to what extent these and dABs are correlated and/or provide independent information.

We are aware of one publication reporting associations between dABs and knee pain where knees with dABs larger than the

Table IV
Relationship between different phenotypes (cartilage-loss-type vs intra-chondral-osteophyte-type) of dABs within those with dABs ($n = 245$). Values are presented as PR with adjustment for age, sex, BMI

	Reference: Exclusive intra-chondral-osteophyte-type dAB* ($n = 124$)	Exclusive cartilage-loss-type dABs† ($n = 58$) PR (95% CI)	Unspecific cartilage-loss-type dABs‡ ($n = 121$) PR (95% CI)
Weightbearing knee pain	1	1.22 (0.80–1.86)	1.35 (0.98–1.87)
P-value (crude)		0.359	0.066
Non-weightbearing knee pain	1	1.80 (0.91–3.55)	1.58 (0.88–2.84)
P-value (crude)		0.090	0.129
Moderate-to-severe knee pain	1	1.20 (0.80–1.81)	1.08 (0.77–1.52)
P-value (crude)		0.382	0.641
Infrequent knee pain	1	0.98 (0.85–1.13)	1.07 (0.94–1.22)
P-value (crude)		0.745	0.341
Frequent knee pain	1	1.00 (0.88–1.14)	1.13 (1.00–1.27)
P-value (crude)		0.950	0.050

* Knees with at least one intra-chondral-osteophyte-type dAB (not combined with cartilage-loss-type dABs) in the femorotibial joint.
† Knees with at least one cartilage-loss-type dAB (not combined with intra-chondral-osteophyte-type dABs) in the femorotibial joint.
‡ Knees with at least one cartilage-loss-type dAB (including the possibility of a combination of cartilage-loss-type and intra-chondral-osteophyte-type dABs).

Table V
Relationship between location (medial and lateral tibia and central femur) of dABs within those with dABs ($n = 245$). Values are presented as PR with adjustment for age, sex, BMI. Reference groups were those with at least one dAB in the femorotibial joint but without any dAB in the respective cartilage plate

	Reference: No dAB in cMF ($n = 151$)	At least one dAB in cMF ($n = 94$) PR (95% CI)	Reference: No dAB in cLF ($n = 156$)	At least one dAB in cLF ($n = 89$) PR (95% CI)
Weightbearing knee pain	1	1.28 (0.94–1.76)	1	0.99 (0.71–1.36)
P-value (crude)		0.119		0.931
Non-weightbearing knee pain	1	1.20 (0.70–2.05)	1	0.51 (0.26–0.97)
P-value (crude)		0.517		0.040
Moderate-to-severe knee pain	1	1.16 (0.83–1.61)	1	0.99 (0.70–1.39)
P-value (crude)		0.396		0.931
Infrequent knee pain	1	1.13 (0.99–1.29)	1	0.92 (0.81–1.06)
P-value (crude)		0.076		0.246
Frequent knee pain	1	1.22 (1.08–1.38)	1	0.95 (0.84–1.07)
P-value (crude)		0.001		0.355
	Reference: No dAB in MT ($n = 155$)	At least one dAB in MT ($n = 90$) PR (95% CI)	Reference: No dAB in LT ($n = 129$)	At least one dAB in LT ($n = 116$) PR (95% CI)
Weightbearing knee pain	1	1.23 (0.90–1.69)	1	1.09 (0.80–1.49)
P-value (crude)		0.203		0.588
Non-weightbearing knee pain	1	1.65 (0.96–2.83)	1	0.87 (0.51–1.50)
P-value (crude)		0.071		0.662
Moderate-to-severe knee pain	1	1.31 (0.94–1.82)	1	0.95 (0.68–1.32)
P-value (crude)		0.113		0.746
Infrequent knee pain	1	1.00 (0.88–1.15)	1	1.13 (0.99–1.29)
P-value (crude)		0.950		0.076
Frequent knee pain	1	1.06 (0.93–1.20)	1	1.15 (1.02–1.30)
P-value (crude)		0.371		0.024

cMF/cLF = central medial/lateral femur.

median size in the patellar and the medial, but not the lateral, femorotibial compartment had more frequent and moderate-to-severe knee pain than those without dABs, also after adjusting for age, sex, BMI and the presence of BMLs [14]. The previous study and our study were similar in the cross-sectional design and in the methodology used to detect and quantify dABs however, our sample size was three times larger, we used a more detailed description of dABs and we extended the pain analysis. In agreement with Moisio *et al.*[14], we found a significant relation between frequent and moderate-to-severe ipsi-lateral knee pain and a presence of dABs however, we found this relation regardless of dAB size. In extension of previous findings, we could also identify a relation between weightbearing, but not non-weightbearing knee pain in those with dABs. Interestingly, the relation between all measures of knee pain, except non-weightbearing knee pain, was stronger when the dAB was located in a central (i.e., weightbearing) subregion and when more than 10% of the central subregion was denuded. These findings are interesting since it is well known that articular cartilage is aneural and thereby insensate to mechanical stimuli[39]. It is also unclear whether intra-chondral-osteophytes are formed by protrusion of the richly innervated subchondral bone or if they are formed by other processes. Although neurovascular invasion of osteophytes were suggested in OA[10], firm relations between the presence of osteophytes and ipsi-lateral knee pain are lacking[17,19,40–42]. On the other hand, subchondral bone has been shown to undergo osteochondral turnover with sensory nerve fibres breaching from the subchondral bone into adjacent layers of non-calcified articular cartilage during OA progression[10,24–26] and the mechanism driving pain remains unclear. It is also not known whether dABs in fact contribute to the pain experience or if they are a manifestation of disease severity, relating to knee pain only indirectly. Still, the positive relationship between dABs and ipsi-lateral knee pain found here, and before[14], suggests that dABs may play one role for different aspects of knee pain in OA however, properly designed longitudinal studies need to confirm such relations.

Cartilage-loss-type dABs, as visualized on MR images, were shown to be highly associated with knee pain in both young and elderly individuals[43,44]. Moreover, our study shows that subjects with moderately denuded central subregions have a higher prevalence of reporting weightbearing, but not non-weightbearing, knee pain than do individuals with only peripheral dABs. Such prevalence was however not found when comparing individuals with moderately and mildly denuded central subregions. This finding is interesting since central subregions of the femorotibial joint are more exposed to peak loads under weightbearing conditions[22,45], in part due to the lack of the protective meniscal tissue. One possible explanation could be that pain is produced from the exposed subchondral bone, independent of the size of the dAB, which may explain the reduced mobility and the limited range of motion seen in knee OA patients. The results of this study generate the hypothesis that both phenotypes and the location (but not the size) of dABs play a role in OA related knee pain.

Having dABs in the central medial femur, but not in any other cartilage plate, slightly increased the prevalence of frequent knee pain compared to having a dAB at another location. The central medial femur was not the plate most frequently affected by dABs[27], but interestingly, this specific location was reported to show the greatest longitudinal change in cartilage thickness and volume amongst the femorotibial cartilage plates[33,46,47]. In addition, the central medial femur was reported to display cartilage thickening at early stages of OA disease, particularly in the external subregion[48]. Although no linkage between pain and cartilage morphology changes has been established, our results agree with other reports in suggesting that the central medial femur might be an important location in knee OA.

Conclusion

This study confirms, in a large sample, the association between the presence of dABs and various important aspects of ipsi-lateral knee pain. One must keep in mind that some of the subjects

without dABs also suffered from knee pain; clearly, therefore, a number of reasons (not all studied here) exist why some have or develop knee pain. However, the purpose of the current work was to focus on dABs, a relatively novel structural correlate of pain. Our extended analysis suggests that subjects with femorotibial dABs encounter significantly more frequent, more moderate-to-severe, and specifically more weightbearing ipsi-lateral knee pain than those without dABs. This relationship appears to be stronger for dABs located in central subregions and for dABs covering more than 10% of a central subregion. Finally, presence of cartilage-loss-type dABs seems to increase the likelihood of frequent ipsi-lateral knee pain, compared to that of intra-chondral-osteophyte-type dABs.

Contributions

Study design and study protocol: SC, MN, KK, FE, RBF.
Data collection: SC, MN, WW, KK, FE, RBF.
Statistical analysis plan: SC, MN, WW, WH, KK, FE, RBF.
Data analysis: SC, MN, KK, FE, RBF.
Manuscript writing: SC, RBF.
Manuscript review: SC, BTW, OB, DD, MN, JG, WW, WH, KK, FE, RBF.
Approval of final manuscript version: SC, BTW, OB, DD, MN, JG, WW, WH, KK, FE, RBF.
All authors agreed to publish and have approved this final version.

Conflict of interests

The image analysis of this study was funded by an industry consortium consisting of Pfizer Inc., Eli Lilly & Co, Merck Serono SA – Geneva, Switzerland, GlaxoSmithKline, and Centocor Inc.
Sebastian Cotofana and Wolfgang Wirth have part time appointments with Chondrometrics GmbH. Felix Eckstein is CEO and co-owner of Chondrometrics GmbH, a company providing MR image analysis services to researchers in academia and industry. He provides consulting services to Pfizer, Merck Serono, Wyeth and Nordo Nordisk. Brad Wyman and Jennifer Gardiner are employed by Pfizer Inc., Olivier Benichou by Eli Lilly & Co, Donatus Dreher by Merck Serono SA. Richard Frobell and Michael Nevitt have no competing interest.
The OAI is a public–private partnership comprised five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Pfizer Inc.; Novartis Pharmaceuticals Corporation; Merck Research Laboratories; and GlaxoSmithKline. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health. This manuscript has received the approval of the OAI Publications Committee based on a review of its scientific content and data interpretation.

Acknowledgement

We would like to thank the readers at Chondrometrics GmbH for dedicated data segmentation.

References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006;367:1747–57.
2. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, *et al*. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994;84:351–8.
3. Colloca L, Benedetti F. How prior experience shapes placebo analgesia. Pain 2006;124:126–33.
4. Deshields TL, Tait RC, Gfeller JD, Chibnall JT. Relationship between social desirability and self-report in chronic pain patients. Clin J Pain 1995;11:189–93.
5. Zubieta JK, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM, *et al*. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. Science 2001;293:311–5.
6. Giardino ND, Jensen MP, Turner JA, Ehde DM, Cardenas DD. Social environment moderates the association between catastrophizing and pain among persons with a spinal cord injury. Pain 2003;106:19–25.
7. Villemure C, Slotnick BM, Bushnell MC. Effects of odors on pain perception: deciphering the roles of emotion and attention. Pain 2003;106:101–8.
8. Birnbaum K, Prescher A, Hessler S, Heller KD. The sensory innervation of the hip joint – an anatomical study. Surg Radiol Anat 1997;19:371–5.
9. Mapp PI. Innervation of the synovium. Ann Rheum Dis 1995;54:398–403.
10. Suri S, Gill SE, Massena dC, Wilson D, McWilliams DF, Walsh DA. Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. Ann Rheum Dis 2007;66:1423–8.
11. Hunter DJ, Lo GH, Gale D, Grainger AJ, Guermazi A, Conaghan PG. The reliability of a new scoring system for knee osteoarthritis MRI and the validity of bone marrow lesion assessment: BLOKS (Boston Leeds Osteoarthritis Knee Score). Ann Rheum Dis 2008;67:206–11.
12. Torres L, Dunlop DD, Peterfy C, Guermazi A, Prasad P, Hayes KW, *et al*. The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. Osteoarthritis Cartilage 2006;14:1033–40.
13. Hill CL, Gale DG, Chaisson CE, Skinner K, Kazis L, Gale ME, *et al*. Knee effusions, popliteal cysts, and synovial thickening: association with knee pain in osteoarthritis. J Rheumatol 2001;28:1330–7.
14. Moisio K, Eckstein F, Chmiel JS, Guermazi A, Prasad P, Almagor O, *et al*. Denuded subchondral bone and knee pain in persons with knee osteoarthritis. Arthritis Rheum 2009;60:3703–10.
15. Lo GH, McAlindon TE, Niu J, Zhang Y, Beals C, Dabrowski C, *et al*. Bone marrow lesions and joint effusion are strongly and independently associated with weight-bearing pain in knee osteoarthritis: data from the osteoarthritis initiative. Osteoarthritis Cartilage 2009;17:1562–9.
16. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol 2000;27:1513–7.
17. Neogi T, Felson D, Niu J, Nevitt M, Lewis CE, Aliabadi P, *et al*. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. BMJ 2009;339:b2844.
18. Sowers MF, Hayes C, Jamadar D, Capul D, Lachance L, Jannausch M, *et al*. Magnetic resonance-detected subchondral bone marrow and cartilage defect characteristics associated with pain and X-ray-defined knee osteoarthritis. Osteoarthritis Cartilage 2003;11:387–93.
19. Kornaat PR, Bloem JL, Ceulemans RY, Riyazi N, Rosendaal FR, Nelissen RG, *et al*. Osteoarthritis of the knee: association between clinical features and MR imaging findings. Radiology 2006;239:811–7.
20. Link TM, Steinbach LS, Ghosh S, Ries M, Lu Y, Lane N, *et al*. Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. Radiology 2003;226:373–81.

21. Phan CM, Link TM, Blumenkrantz G, Dunn TC, Ries MD, Steinbach LS, *et al*. MR imaging findings in the follow-up of patients with different stages of knee osteoarthritis and the correlation with clinical symptoms. Eur Radiol 2006;16:608–18.
22. Eckstein F, Ateshian G, Burgkart R, Burstein D, Cicuttini F, Dardzinski B, *et al*. Proposal for a nomenclature for magnetic resonance imaging based measures of articular cartilage in osteoarthritis. Osteoarthritis Cartilage 2006;14:974–83.
23. Buck RJ, Wyman BT, Le Graverand MP, Wirth W, Eckstein F. An efficient subset of morphological measures for articular cartilage in the healthy and diseased human knee. Magn Reson Med 2010;63:680–90.
24. Suri S, Walsh DA. Osteochondral alterations in osteoarthritis. Bone 2012;51:204–11.
25. Nixon AJ, Cummings JF. Substance P immunohistochemical study of the sensory innervation of normal subchondral bone in the equine metacarpophalangeal joint. Am J Vet Res 1994;55:28–33.
26. Walsh DA, McWilliams DF, Turley MJ, Dixon MR, Franses RE, Mapp PI, *et al*. Angiogenesis and nerve growth factor at the osteochondral junction in rheumatoid arthritis and osteoarthritis. Rheumatology (Oxford) 2010;49:1852–61.
27. Frobell RB, Wirth W, Nevitt M, Wyman BT, Benichou O, Dreher D, *et al*. Presence, location, type and size of denuded areas of subchondral bone in the knee as a function of radiographic stage of OA – data from the OA initiative. Osteoarthritis Cartilage 2010;18:668–76.
28. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007;15(Suppl A): A1–A56.
29. Burgkart R, Glaser C, Hyhlik-Durr A, Englmeier KH, Reiser M, Eckstein F. Magnetic resonance imaging-based assessment of cartilage loss in severe osteoarthritis: accuracy, precision, and diagnostic value. Arthritis Rheum 2001;44:2072–7.
30. Graichen H, von Eisenhart-Rothe R, Vogl T, Englmeier KH, Eckstein F. Quantitative assessment of cartilage status in osteoarthritis by quantitative magnetic resonance imaging: technical validation for use in analysis of cartilage volume and further morphologic parameters. Arthritis Rheum 2004;50:811–6.
31. Eckstein F, Buck RJ, Burstein D, Charles HC, Crim J, Hudelmaier M, *et al*. Precision of 3.0 Tesla quantitative magnetic resonance imaging of cartilage morphology in a multicentre clinical trial. Ann Rheum Dis 2008;67:1683–8.
32. Wirth W, Hellio Le Graverand MP, Wyman BT, Maschek S, Hudelmaier M, Hitzl W, *et al*. Regional analysis of femorotibial cartilage loss in a subsample from the Osteoarthritis Initiative progression subcohort. Osteoarthritis Cartilage 2009;17:291–7.
33. Eckstein F, Maschek S, Wirth W, Hudelmaier M, Hitzl W, Wyman B, *et al*. One year change of knee cartilage morphology in the first release of participants from the Osteoarthritis Initiative progression subcohort: association with sex, body mass index, symptoms and radiographic osteoarthritis status. Ann Rheum Dis 2009;68:674–9.
34. Eckstein F, Hudelmaier M, Wirth W, Kiefer B, Jackson R, Yu J, *et al*. Double echo steady state magnetic resonance imaging of knee articular cartilage at 3 Tesla: a pilot study for the Osteoarthritis Initiative. Ann Rheum Dis 2006;65:433–41.
35. Wirth W, Eckstein F. A technique for regional analysis of femorotibial cartilage thickness based on quantitative magnetic resonance imaging. IEEE Trans Med Imaging 2008;27:737–44.
36. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
37. Stratford PW, Kennedy DM, Woodhouse LJ, Spadoni GF. Measurement properties of the WOMAC LK 3.1 pain scale. Osteoarthritis Cartilage 2007;15:266–72.
38. Ornetti P, Dougados M, Paternotte S, Logeart I, Gossec L. Validation of a numerical rating scale to assess functional impairment in hip and knee osteoarthritis: comparison with the WOMAC function scale. Ann Rheum Dis 2011;70:740–6.
39. Dye SF, Vaupel GL, Dye CC. Conscious neurosensory mapping of the internal structures of the human knee without intra-articular anesthesia. Am J Sports Med 1998;26:773–7.
40. Lanyon P, O'Reilly S, Jones A, Doherty M. Radiographic assessment of symptomatic knee osteoarthritis in the community: definitions and normal joint space. Ann Rheum Dis 1998;57:595–601.
41. O'Reilly SC, Muir KR, Doherty M. Screening for pain in knee osteoarthritis: which question? Ann Rheum Dis 1996;55:931–3.
42. Sengupta M, Zhang YQ, Niu JB, Guermazi A, Grigorian M, Gale D, *et al*. High signal in knee osteophytes is not associated with knee pain. Osteoarthritis Cartilage 2006;14:413–7.
43. Zhai G, Blizzard L, Srikanth V, Ding C, Cooley H, Cicuttini F, *et al*. Correlates of knee pain in older adults: Tasmanian Older Adult Cohort Study. Arthritis Rheum 2006;55:264–71.
44. Zhai G, Cicuttini F, Ding C, Scott F, Garnero P, Jones G. Correlates of knee pain in younger subjects. Clin Rheumatol 2007;26:75–80.
45. Bingham JT, Papannagari R, Van de Velde SK, Gross C, Gill TJ, Felson DT, *et al*. In vivo cartilage contact deformation in the healthy human tibiofemoral joint. Rheumatology (Oxford) 2008;47:1622–7.
46. Eckstein F, Wirth W, Hudelmaier M, Stein V, Lengfelder V, Cahue S, *et al*. Patterns of femorotibial cartilage loss in knees with neutral, varus, and valgus alignment. Arthritis Rheum 2008;59:1563–70.
47. Hunter DJ, Niu J, Zhang Y, Totterman S, Tamez J, Dabrowski C, *et al*. Change in cartilage morphometry: a sample of the progression cohort of the Osteoarthritis Initiative. Ann Rheum Dis 2009;68:349–56.
48. Buck RJ, Wyman BT, Le Graverand MP, Hudelmaier M, Wirth W, Eckstein F. Does the use of ordered values of subregional change in cartilage thickness improve the detection of disease progression in longitudinal studies of osteoarthritis? Arthritis Rheum 2009;61:917–24.